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ISMP Adverse Drug Reactions: Pheochromocytoma Crisis Induced by Metoclopramide Baclofen Dependence Following High-Dose Therapy Fatal Cardiotoxicity Following High-Dose Cyclophosphamide Acute Anterograde Amnestic Syndrome Induced by Fentanyl Ivermectin-Induced Toxic Epidermal Necrolysis Pembrolizumab-Induced Type 1 Diabetes

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA) MedWatch program (800-FDA-1088). If you have reported an interesting, preventable ADR to MedWatch, please consider sharing the account with our readers. E-mail Dr. Mancano at michael.mancano@temple.edu. Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MedWatch program and Temple University School of Pharmacy. ISMP is an FDA MedWatch partner.

Pheochromocytoma Crisis Induced by Metoclopramide

A 36-year-old woman with past medical history significant for anxiety and obesity was observed in the emergency department (ED) with complaints of headaches, nausea, and vomiting for the preceding 3 days. Her vital signs were normal, apart from a slightly elevated blood pressure (BP) of 134/86 mm Hg, and her physical and neurological examinations were both unremarkable, including a computed tomographic (CT) scan of her head. Metoclopramide 10 mg was administered intravenously for symptomatic management of the patient's nausea and headaches. One hour after administration, the patient reported severe agitation and headache, ranking her pain 9 out of 10 on a pain scale, and the patient's BP increased to 223/102 mm Hg. Diphenhydramine and methylprednisolone were administered, after suspecting an allergy to metoclopramide, and labetalol and hydralazine were administered to decrease BP. Laboratory findings drawn after administration of metoclopramide appeared normal, except for leukocytosis (White Blood Cell Count, 14.3K/μL; normal, 4-11K/μL). Severe left-sided chest pain and diaphoresis manifested two and a half hours later, and a wide-complex tachycardia with a heart rate of 177 bpm was observed on electrocardiogram (ECG). Given the new progression of symptoms, aortic dissection was suspected, and the patient underwent a CT scan of her chest and abdomen, which showed a large heterogeneous right adrenal mass, with no other acute findings.

The patient's symptoms further progressed, after completion of the CT scan, to acute respiratory distress with hypoxia and central cyanosis, with repeated episodes of vomiting; the patient was later intubated to protect the airway. Metabolic acidosis with severe acidemia (pH $<$6.81, normal, 7.35-7.45), as well as lactic acidosis (16.4 mmol/L, normal, 0.5-1 mmol/L) developed. Progressing acute respiratory distress syndrome requiring extracorporeal membrane oxygenation (ECMO) precipitated her transfer to a tertiary care center. The patient's status further declined, suffering non-ST segment elevation myocardial infarction, cardiogenic shock, acute liver failure with an aspartate aminotransferase of

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13,794 U/L (normal range, 10-30 U/L), alanine aminotransferase of 10,569 U/L (normal range, 10-40 U/L), international normalized ratio of 3.4 (normal range, 1-1.3), and oliguric renal failure requiring continuous renal replacement therapy (SrCr 3.08 mg/dL, normal, 0.5-1.1 mg/dL in adult females). Plasma metanephrines were severely elevated, with metanephrine of 543 nmol/L (normal, <0.9 nmol/L) and normetanephrine at 443 nmol/L (normal, <0.5 nmol/L). Elevated plasma metanephrines are the preferred diagnostic biomarker for suspected pheochromocytoma, suggesting pheochromocytoma as the likely diagnosis of the patient's large adrenal mass. Pheochromocytoma was confirmed after surgical removal of the mass on hospital day 27. No further status of the patient's condition was provided post surgery.

The authors[1] point out that metoclopramide-induced hypertensive crisis in pheochromocytoma has been described in the medical literature. This is caused by the catecholamine-releasing effect of metoclopramide in patients with pheochromocytoma. Historically, D2 receptor antagonism was thought to be responsible, but more recent evidence suggests that the 5-HT4 receptors also play an important role. The authors report this case as an important reminder that metoclopramide, a frequently used medication in the ED, can trigger acute pheochromocytoma crisis.

Baclofen Dependence Following High-Dose Therapy

Baclofen is a $GABA_B$ receptor agonist most commonly used to treat muscle spasticity, but when used in high doses may also be used in the treatment of treatment-resistant alcohol dependence. Despite conflicting reports in the literature regarding the effectiveness of baclofen for the treatment of alcohol dependence, the French health authority approved its use for this indication in March 2014.

A 63-year-old woman was hospitalized after suffering a loss of consciousness. Upon admission, the patient reported a dizziness, headache, disorientation to space and time, and worsening vomiting episodes over the preceding 2 months. For 6 months, the patient had been treated with gradually increasing doses of baclofen for alcohol dependence to eventually reach a dose of 90 mg 3 times daily. The patient's medical history was significant for anxiety, depression, and a sleep disorder, managed with a regimen of escitalopram 10 mg daily, zopiclone 7.5 mg daily at bedtime, and oxazepam 12.5 mg daily; further, the patient also had uncontrolled hypertension, for which she received no treatment. On admission, vital signs and physical examination findings were normal, except for an elevated BP of 200/130 mm Hg. The patient had additional subjective complaints of widespread pain, dyspepsia, difficulty with visual accommodation, excessive tiredness, and insomnia. Neurological, cardiovascular, and pulmonary findings were normal, apart from an elevated BP. There was no alcohol in the patient's blood, and the patient reported abstinence for 2 months.

Baclofen was discontinued, given the likelihood of baclofen toxicity at extremely high doses, and nicardipine was administered intravenously to lower the BP. The patient had been kept overnight for observation, when 4 days later, she presented with severe anxiety, visual hallucinations, and confusion. Clinicians ruled out alcohol withdrawal, given the patient's prolonged abstinence from alcohol, and increased oxazepam to 62.5 mg daily for symptomatic relief. After the patient felt no relief of her symptoms, baclofen was reintroduced at a daily dose of 30 mg, prompting immediate relief of the patient's anxiety and agitation. After a few days of observation in the hospital, the patient was discharged on baclofen 10 mg 3 times daily, escitalopram 10 mg daily, oxazepam 12.5 daily, nicardipine if needed, and daily vitamin B_1 and B_6 supplementation.

The authors[2] highlight the peculiarity of a withdrawal syndrome that can only be managed with the exact agent that was removed in the first place, rather than with benzodiazepines, which are often used to treat alcohol withdrawal symptoms. Given that baclofen is a $GABA_B$ agonist, whereas benzodiazepines, as a class, are $GABA_A$ agonists, the authors suggest that these drugs would not alone be sufficient to treat baclofen withdrawal syndrome. Last, it is important to note the potential for dependence with baclofen, especially when used at extremely high doses. It is reasonable to have a conversation between patient and clinician regarding these risks before and throughout therapy.

Fatal Cardiotoxicity Following High-Dose Cyclophosphamide

A 54-year-old woman with no significant medical history was diagnosed with systemic sclerosis 2 years prior. Systemic sclerosis is an autoimmune connective tissue disease characterized by fibrosis in skin and internal organs, damage to vasculature, and autoantibody formation. Due to worsening skin fibrosis and increasing pulmonary involvement, the patient was referred for autologous hematopoietic stem cell transplantation (ASCT) with high-dose cyclophosphamide. Prior to transplantation, an extensive and comprehensive cardiopulmonary examination was performed and found to be normal, including physiologic, laboratory, radiological, and ECG.

Peripheral hematopoietic stem cells were mobilized with cyclophosphamide (3 g/m^2 total daily dose, given over 2 consecutive days) and filgrastim (10 μg/kg/d for 5 days). After collection and cytapheresis, clinicians harvested 8.58×10^6 CD34+ cells/kg in one round, and froze the cells in DMSO 10% and albumin 4%. The patient was not experiencing extreme toxicity or cardiovascular concerns.

The patient returned 1 month later for conditioning therapy and to receive her ASCT, so cardiopulmonary markers were examined. The patient had a normal left ventricular ejection fraction (LVEF) of 63%, and troponins and other laboratory findings were in the normal range. Conditioning therapy involved administration of intravenous cyclophosphamide

(200 mg/kg over 4 consecutive days) 12 grams administered over 4 days, hydration therapy with 2 L of IV normal saline per day, intravenous rabbit antithymocyte globulins (2.5 mg/kg/d over 3 consecutive days). In addition to conditioning therapy, harvested CD34+ cells were thawed and reinfused after being washed twice, to remove the maximal amount of DMSO possible.

Within 12 hours after ASCT, progressive acute pulmonary edema developed and intravenous diuretics were administered for management. Ten hours later, signs of worsening acute pulmonary edema appeared, with the patient complaining of anterior chest pain and difficulty breathing, and confirmed on chest radiograph and ECG. On examination, the patient had decreasing BP of 90/45 mm Hg, a heart rate of 130 bpm, bilateral crackles, and an O_2 saturation of 89% on room air. Laboratory findings showed Troponin Ic of 9.59 μg/L (normal range, ≤0.04 μg/L) and B-type Natriuretic Peptide (BNP) of 7136 ng/L (normal range, ≤100 ng/L), and LVEF was <10% on echocardiogram. Clinicians suspected cyclophosphamide-induced cardiotoxicity, and the patient was transferred to the intensive care unit. Shortly thereafter, the patient suffered cardiac arrest, and despite supportive therapy involving dobutamine and heparin, the patient showed no improvement in her cardiovascular condition. A thrombus formed in the left side of her heart, extending into the pulmonary vein; concurrently, an intracranial hemorrhage formed, posing a contraindication to the intensive anticoagulation needed to treat the clot in her heart. The patient died within 24 hours. On autopsy, the heart exhibited signs of hemorrhagic pericarditis, thrombus formation, extending to the pulmonary veins and the inferior vena cava. The authors[3] noted these findings supported cyclophosphamide-induced cardiotoxicity as the likely cause of death.

The authors state that this case represents the first report of histologically proven cyclophosphamide-related cardiotoxicity in a patient receiving ASCT for an autoimmune disease. Reports of cyclophosphamide-mediated cardiotoxicity in the literature are almost exclusively related to the drug's use in cancer patients, when used concomitantly with other cardiotoxic medications. Although the authors intended to take utmost precautions and completed an extremely comprehensive examination of the patient's cardiovascular health, this toxicity still manifested, suggesting the seeming unpredictability of this reaction. Fortunately, the authors posit that acute cyclophosphamide-induced cardiotoxicity is very rare; nonetheless, further research is certainly warranted.

Acute Anterograde Amnestic Syndrome Induced by Fentanyl

The authors[4] evaluated a total of 14 patients that had an acute anterograde amnestic syndrome in Massachusetts between 2012 and 2016, and noted 13 tested positive for opioids on a toxicological screen or had a history of opioid use, but none of them underwent testing for synthetic opioids such as fentanyl. Anterograde amnesia is a loss of the ability to create new memories after the event that caused amnesia, leading to a partial or complete inability to recall the recent past, while long-term memories from before the event remain intact. The acute anterograde amnestic syndrome described in these patient cases lasted for months or longer and was characterized by a hyperintense signal involving both hippocampi on magnetic resonance imaging diffusion-weighted sequences. There were also variably observed deficits in other cognitive domains such as orientation and attention.

In 2017, there was a patient with a history of heroin use that experienced this amnestic syndrome after overdosing in Maryland, who was later transferred to a tertiary care center in West Virginia, and tested positive for the fentanyl metabolite norfentanyl and cocaine. In addition, there were 4 patients with a history of heroin use (ages ranging 28 to 37 years) who presented with the same amnestic syndrome in Massachusetts who all tested positive for fentanyl and norfentanyl (3 confirmed by urine fentanyl level 1.8 to >200 ng/mL and 1 confirmed by serum fentanyl level 1.87 ng/mL.

The authors suggest that interpretation of the cause of the amnestic syndrome is limited because another unidentified drug, adulterant, or contaminant that was not tested for may be the cause of the amnestic syndrome. However, the authors feel that the confirmed presence of fentanyl in the 4 patients, and the fact that in 2 of the 4 patients fentanyl was the only drug detected strengthens the association of fentanyl and this syndrome, and the authors feel that this syndrome is being observed in patients now because of the increasing presence of fentanyl in illicit drugs. The authors end by suggesting an expanded toxicologic screening for fentanyl and its analogues in patients with a history of substance use who present with this amnestic syndrome.

Ivermectin-Induced Toxic Epidermal Necrolysis

A 45-year-old man presented with worsening rash involving his entire body 3 days after taking 15 mg of ivermectin, which was ordered in the ED for suspected body lice. On examination, the patient had oral blisters, conjunctivitis, and a generalized erythematous maculopapular rash involving his entire body with denudation of the skin on his back. The patient tested negative for HIV, hepatitis A, B, and C, urine toxicology screen, autoimmune screen, and rapid plasma regain. Skin biopsy and further pathological examination showed acute vacuolar interface dermatitis with many cytoids and epidermal necrosis consistent with toxic epidermal necrolysis (TEN). The patient received supportive care and made an unremarkable recovery with no long-term sequelae. Based on the Naranjo algorithm, the patient scored 7 out of 10 which supports the assessment that this was a drug-related adverse event.

The authors[5] note that TEN is a rare, severe, cutaneous adverse reaction that can be fatal. The average mortality rate of TEN is 25% to 35% but can be higher in elderly patients

and those with a large surface area of epidermal detachment. Of those that survive, majority of patients suffer from long-term complications of the disease. The pathogenesis of TEN is not completely understood, but 2 proposed mechanisms are (1) drug-induced cytotoxicity mediated by lymphocytes and keratinocyte cell death, or (2) metabolites produced by isozyme CYP3A4. The authors recommend that since ivermectin is a commonly used antiparasitic drug, increased awareness among healthcare professionals regarding TEN is critical. Furthermore, although rare, clinicians should educate their patients of this adverse event, so that the patients might seek medical help and discontinue the medication as soon as possible if rash were to occur.

Pembrolizumab-Induced Type 1 Diabetes

A 61-year-old Caucasian woman with no history of diabetes diagnosed with confirmed cholangiocarcinoma which was found to be surgically unresectable. The patient underwent treatment with chemoradiation including 5-fluoruracil. After 3 years of surveillance, the patient was found to have persistent hyponatremia though to be secondary to paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH). A CT scan showed multiple pulmonary nodules and a biopsy of one nodule confirmed metastatic cholangiocarcinoma, so the patient was enrolled in a Phase II clinical study and completed 8 cycles of folinic acid, fluorouracil and oxaliplatin (FOLFOX), and 6 concurrent cycles of pembrolizumab (Keytruda) starting on cycle 3. The patient experienced fatigue, nausea, and vomiting despite a dose reduction of 60% on cycle 6. After the sixth cycle, the size of the patient's pulmonary nodules decreased, and her cancer antigen 19.9 level decreased from 94 U/mL to 68 U/mL (reference range, $\leq$37 U/mL).

After completion of the ninth cycle of FOLFOX and pembrolizumab, the patient developed severe nausea, vomiting, fatigue, and abdominal pain. The patient's physical exam was notable for orthostatic hypotension, an emaciated appearance, and fruity breath. Test results showed the patient was hyperglycemic with blood glucose 475 mg/dL (normal range, 70-110 mg/dL), hemoglobin A1c of 8.7% (normal value, $\leq$ 7%), hyponatremic with sodium of 126 mEq/L (normal range, 136-146 mEq/L) with a corrected value of 132 mEq/L, and acidotic with an anion gap of 26 (normal range, 8-16 mEq/L). Renal and liver function was normal, alkaline phosphatase was elevated at 374 U/L (normal range, 30-120 U/L), with a normal lipase. Complete blood counts showed mild neutrophilic leukocytosis but otherwise normal. The patient was started on an insulin drip with presumed diagnosis of diabetic ketoacidosis.

A year prior to presentation, the patient's blood glucose was within normal limits. However, a CT scan a few weeks before presentation showed atrophy of the pancreas. The patient did not have a history of diabetes but 2 of her grandchildren have Type 1 diabetes mellitus. A panel of autoantibodies against islet cell antigens revealed a strongly positive GAD65 antibody $>$250 IU/mL (reference range, 0.0-0.5 IU/mL) but other antibodies were not detected. The patient was treated with methylprednisolone 125 mg intravenously once followed by prednisone 60 mg oral daily tapered over 2 weeks. The patient unfortunately still requires insulin even after the steroid course.

Pembrolizumab is a PD-1 inhibitor that harnesses the body's immune system to fight cancer cells. Cancer cells frequently upregulate the expression of ligands to inhibitory checkpoints (such as PD-1) to evade detection and destruction by the immune system. Checkpoint inhibitors like pembrolizumab re-enable the immune system to find and eliminate cancer cells. Unfortunately, checkpoint inhibitors also cause immune-related adverse effects such as diarrhea, rash, fatigue, pneumonitis, and multiple endocrinopathies including Type 1 diabetes mellitus. Type 1 diabetes mellitus occurs because of an autoimmune destruction of insulin-producing β cells in the islet of Langerhans. Autoantibodies against islet cell antigens (such as insulinoma-associated antigen-1, micro-IAA, zinc transporter 8 and glutamic acid decarboxylase 65 [GAD65]) are used to diagnose Type 1 diabetes mellitus. If diabetes is not controlled, it can lead to life-threatening hyperglycemic hyperosmolar state or diabetic ketoacidosis.

The authors[6] point out that there are currently no established guidelines for treating checkpoint inhibitor associated Type 1 diabetes. Aside from withholding the offending agent, treating with an immunosuppressor like corticosteroids is advised. The patient in the presented case was treated with the institution's standard treatment for checkpoint inhibitor–related toxicity: methylprednisolone 125 mg bolus intravenously once followed by prednisone 1 mg/kg/d orally, but unfortunately, the patient remains insulin dependent. Theoretically, a more aggressive immunosuppressive therapy could be used to save remaining β islet cells, but there are no studies to support this practice for immune-related side effects of immune checkpoint inhibitors. It is also possible that even though there is evidence in murine models demonstrating some regeneration of β islet cells, by the time a patient presents with diabetes, too many β islet cells have been destroyed and even a complete reversal of checkpoint inhibition at that point may not be enough to allow the patient to be insulin independent.

The authors recommend that because there are no established protocols or data to treat and prevent the progression of Type 1 diabetes associated with the use of immune checkpoint inhibitors, it is critical for clinicians using immune checkpoint inhibitors to get a detailed family history and to

weight the benefits in a patient with a high risk of developing a new autoimmune disease. Particularly, patients with a family or personal history of Type 1 diabetes should be closely monitored for life-threatening hyperglycemic hyperosmolar state or diabetic ketoacidosis.

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